

**REMARKS**

The present application was filed on March 17, 2004 with claims 1 through 12. Claim 13 was added in a prior response. Claims 6-9 and 12 were previously cancelled without prejudice. Claims 1-5, 10, 11 and 13 are presently pending in the above-identified patent application, claim 1 being the independent claim.

In the present Office Action, the Examiner objected to claim 3 because of a grammatical error, rejected claims 10-11 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, and rejected claims 1-5 and 10-11 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The comments of the Examiner in forming the rejections are acknowledged and have been carefully considered.

In this response, claim 13 has been cancelled without prejudice as being directed to a non-elected invention. Applicants reserve the right to present the feature(s) recited in claim 13 in one or more divisional applications. Claims 3, 10 and 11 have been amended. Support for these amendments may be found, for example, in paragraphs [0068] and [0070] of the present specification. Furthermore, claim 14 has been added. Claim 14 is dependent from claim 1 and is considered to be a product-by-process claim based thereon. Support for claim 14 may be found in the present specification, for example, on page 14, line 22, to page 18, line 12. Applicants submit that no new matter has been introduced by the amendments made herein.

Applicants respectfully request reconsideration of the present application in view of the above amendments and remarks set forth below.

**Claim Objection**

As noted above, the Examiner has objected to claim 3 because of a grammatical error. In response to this objection, claim 3 has been amended to replace the recitation “iinsert” with “insert.” Applicants respectfully submit that claim 3, as amended, overcomes the present objection thereto. Accordingly, withdrawal of the objection to claim 3 is respectfully requested.

§112, second paragraph rejection

As noted above, the Examiner has rejected claims 10 and 11 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, on page 4 of the Office Action, the Examiner contends that:

it is unclear what these specific distances and positions are related to with regards to ubiquitin and barnase.... [the] description lacks sufficient detail as to what these specific positions and distances represent with regards to the specific insert domain positions recited in the claimed invention.

Applicants respectfully disagree with this contention.

More particularly, Applicants assert that the description set forth in the present specification provides sufficient detail with respect to the noted claim elements. By way of example, with respect to the recited amino-carboxyl length, Applicants point to paragraph [0043] of the specification, wherein it is stated that:

[t]he amino terminal of the exemplary insert protein is spatially separated from the carboxyl terminal of the exemplary insert protein by a linear distance known as the amino-carboxyl length (hereinafter, the “N-C terminal length”) of the exemplary insert protein, that is measured when the exemplary insert protein is in its folded conformation. (Emphasis added)

Also, with respect to the noted alpha-carbon-alpha-carbon length, Applicants point again to paragraph [0043] of the specification, wherein it is stated that:

[t]he first surface loop amino acid of the exemplary target protein is spatially separated from the second surface loop amino acid of the exemplary target protein by a linear distance known as the alpha-carbon-alpha-carbon length of the surface loop of the exemplary target protein (hereinafter, the “C $\alpha$ -C $\alpha$  length”), that is also measured when the exemplary target protein is in its folded conformation. (Emphasis added)

Further, by way of example, paragraph [0069] of the present specification states that:

[t]he exemplary insert protein ubiquitin and the exemplary target protein barnase satisfy the novel structural design criterion that the N-C terminal length of the exemplary insert protein be at least twice the C $\alpha$ -C $\alpha$  length of the exemplary target protein surface loop selected for insertion.

Additionally, with respect to the numbered positions, Applicants point to paragraph [0068] of the specification, wherein it is stated, for example, that “the ubiquitin molecule, shown in

FIG. 2A, is inserted between amino acid residue 66 and amino acid 67 of barnase.”  
(Emphasis added)

Applicants respectfully assert that the present specification provides, to one having skill in the art, sufficient detail as to what these specific positions and distances represent with regard to the insert domain positions recited in claim 10, so as to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Moreover, page 4 of the Office Action states that:

[c]laim 11 recites “the controllable first and second effector signals” (lines 4-5). There is a lack of antecedent basis for this limitation, as parent claim 10 does not recite controllable first and second effector signals. It is noted that dependent claim 3 does have antecedent basis for controllable effector signals.

Applicants submit that claim 11, as amended, remedies the alleged antecedent basis issue.

For at least the reasons stated above, Applicants respectfully request withdrawal of the rejection of claims 10 and 11 under 35 U.S.C. §112, second paragraph.

§112, first paragraph, rejection

As noted above, the Examiner has rejected claims 1-5 and 10-11 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner contends, page 6 of the Office Action, that:

[g]iven that the genus for ubiquitin proteins essentially includes all ubiquitin genes of any length, and given that the claims are not limited to any specific region of the ubiquitin gene within the barnase target protein, it is unclear what domain of ubiquitin is actually inserted into the barnase target protein.... Therefore one of ordinary skill in the art would have reasonable doubt as to what length of ubiquitin insert protein is inserted into the barnase target protein....

Applicants respectfully disagree with this contention and assert that the present specification provides sufficient detail so as to enable one skilled in the art to which the invention pertains to make and use the same, in compliance with 35 U.S.C. §112, first paragraph.

Specifically, with respect to a ubiquitin domain, paragraph [0041] of the present specification describes “an exemplary insert protein having an insert domain lying between an amino terminal and a carboxyl terminal, which insert domain is associated with a first

quantity of free energy.” Additionally, with respect to the relationship between the insert protein and the target protein, paragraphs [0043] and [0044] of the specification state that:

[t]he amino terminal of the exemplary insert protein is spatially separated from the carboxyl terminal of the exemplary insert protein by a linear distance known as the amino-carboxyl length (hereinafter, the "N-C terminal length") of the exemplary insert protein, that is measured when the exemplary insert protein is in its folded conformation. The first surface loop amino acid of the exemplary target protein is spatially separated from the second surface loop amino acid of the exemplary target protein by a linear distance known as the alpha-carbon-alpha-carbon length of the surface loop of the exemplary target protein (hereinafter, the "Ca-Ca length"), that is also measured when the exemplary target protein is in its folded conformation.

The molecular structure of the exemplary fusion protein is engineered so that, at any time, the folding of the insert domain necessarily unfolds the target domain, and vice versa, thereby making the folded and unfolded states of the insert and target domains mutually exclusive. This mutual exclusion of concurrently folded or concurrently unfolded states is accomplished by the insertion of the exemplary insert protein into the surface loop of the exemplary target protein subject to a novel structural design criterion wherein the N-C terminal length of the exemplary insert protein is at least two-times greater than the Ca-Ca length of the surface loop of the exemplary target protein. (Emphasis added)

The Office Action, on page 6, states that “[t]he specification discloses an example wherein the ubiquitin molecule is inserted between amino acid residue 66 and 67 of barnase..., however this limitation is not recited in claim 10.” Applicants assert, however, that claim 10 has been amended herein to include the aspect of “wherein the insert protein is inserted between amino acid residue 66 and amino acid residue 67 of the target protein.” Accordingly, Applicants respectfully submit that the noted concerns are overcome.

Further, the Office Action, on page 7, states that:

[g]iven applicant’s lack of disclosure for the different types of barnase variants and their functionality at different temperatures, one of ordinary skill in the art would have reasonable doubt that applicants were actually in possession of a fusion protein with a barnase target domain that functioned for all barnase protein variants....

Applicants note, however, that independent claim 1 includes the limitation of “a barnase target protein having a surface loop that begins at an alpha carbon of a terminal amino acid of the surface loop and terminates at an alpha carbon of a terminal amino acid of the surface loop, the surface loop comprising a cytotoxic target domain of the barnase target

protein.” Additionally, Applicants assert that an individual domain of the barnase protein is being utilized. By way of illustration, paragraphs [0064] and [0066] of the present specification state:

To create a specific nonlimiting exemplary embodiment of the model for a MEDF switch, the inventors herein created a two-domain bifunctional fusion protein comprising the insertion of an exemplary insert protein, the human ubiquitin molecule having one regulatory domain, into a selected surface loop of an exemplary target protein, barnase, which has one catalytic (or cytotoxic) domain.

....  
The exemplary target protein, barnase is a ribonuclease produced exclusively by the bacterium *Bacillus amyloliquefaciens*. Barnase has one catalytic domain that is functionally cytotoxic to all mammalian cell types. (Emphasis added)

Applicants note that claims 3 and 4 include aspects of the target cytotoxic domain folding under the influence of a first controllable effector signal, wherein such an effector signal can include ligand binding, pH and temperature. See, for example, paragraph [0070] of the present specification. Additionally, paragraph [0068] of the specification details an exemplary barnase molecule within the context of the invention. Further, paragraphs [0072] through [0092] of the specification describe the creation of an exemplary fusion protein as well as experimental procedures and results detailing Applicants’ possession of said fusion protein at the time the application was filed, in compliance with 35 U.S.C. §112, first paragraph.

For at least the reasons given above, Applicants respectfully request withdrawal of the rejection of claims 1-5, 10 and 11 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

With regard to claim 14, which is newly presented herein, Applicants respectfully assert that this claim is patentable by virtue of its dependency from claim 1, which is believed to be patentable for at least the reasons previously stated. Moreover, Applicants submit that this claim recites independently patentable subject matter. Accordingly, favorable consideration and allowance of claim 14 is respectfully solicited.

In view of the foregoing, Applicants submit that all of the pending claims, namely, claims 1-5, 10, 11 and 14, are in condition for allowance, and such favorable action thereon is respectfully solicited.

If any outstanding issue(s) remain, in the interest of expediting allowance of the present application the Examiner is invited to contact the undersigned attorney at the telephone number indicated below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Wayne L. Ellenbogen", with a long horizontal flourish extending to the right.

Date: October 19, 2009

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